

ITW

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Date

*March 21, 2007*

*Jennifer A. [Signature]*

Attorney Docket No. 100717-688 KGB  
Confirmation No.

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

APPLICANT : Alexander AZZAWI et al ✓  
SERIAL NO. : 10/583,524  
CUSTOMER NO. : 27384  
FILED : June 16, 2006  
FOR : METHOD AND DEVICE FOR MARKING  
BIOMOLECULES  
ART UNIT : To Be Assigned  
EXAMINER : To Be Assigned

Commissioner for Patents  
PO Box 1450  
Alexandria, VA 22313-1450

**TRANSMITTAL OF ENGLISH TRANSLATION OF THE  
INTERNATIONAL SEARCH REPORT**

SIR:

Appended hereto is an English translation of the International Search Report.

Applicant requests that this document be made of record in the above identified application.

Respectfully submitted,  
NORRIS McLAUGHLIN & MARCUS, P.A.

By

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**PCT**

NOTIFICATION OF TRANSMITTAL  
OF COPIES OF TRANSLATION  
OF THE INTERNATIONAL PRELIMINARY REPORT  
ON PATENTABILITY  
(CHAPTER I OR CHAPTER II  
OF THE PATENT COOPERATION TREATY)  
(PCT Rules 44bis.3(c) and 72.2)

From the INTERNATIONAL BUREAU

**Ausl. Gr.**

To:

SIEGERS, Britta  
c/o Bayer Business Services GmbH  
Law and Patents  
Patents and Licensing  
51368 Leverkusen  
ALLEMAGNE

Bayer AG  
Bayer Business Services  
Law and Patents

14. Sep. 2006

**EINGANG**

Date of mailing (day/month/year)

08 September 2006 (08.09.2006)

Applicant's or agent's file reference

EMB 04 1018-WO

**IMPORTANT NOTIFICATION**

International application No.

PCT/EP2004/012172

International filing date (day/month/year)

28 October 2004 (28.10.2004)

Applicant

EHRFELD MIKROTECHNIK BTS GMBH et al

**1. Transmittal of the translation to the applicant.**

The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter I).



The International Bureau transmits herewith a copy of the English translation of the international preliminary report on patentability (Chapter II).

**2. Transmittal of the copy of the translation to the designated or elected Offices.**

The International Bureau notifies the applicant that copies of that translation have been transmitted to the following designated or elected Offices requiring such translation:

None

The following designated or elected Offices, having waived the requirement for such a transmittal at this time, will receive copies of that translation from the International Bureau only upon their request:

AE, AG, AL, AM, AP, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EA, EC, EE, EG, EP, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OA, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW

**3. Reminder regarding translation into (one of) the official language(s) of the elected Office(s).**

The applicant is reminded that, where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability (Chapter II).

It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned within the applicable time limit (Rule 74.1). See Volume II of the PCT Applicant's Guide for further details.

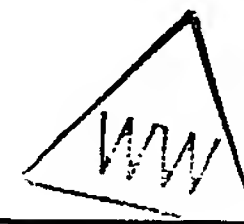
The International Bureau of WIPO  
34, chemin des Colombettes  
1211 Geneva 20, Switzerland

Authorized officer

Yolaine Cussac

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# PATENT COOPERATION TREATY

## PCT

### INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference B 04 1018-WO	<b>FOR FURTHER ACTION</b>		See item 4 below
International application No. T/EP2004/012172	International filing date ( <i>day/month/year</i> ) 28 October 2004 (28.10.2004)	Priority date ( <i>day/month/year</i> ) 20 December 2003 (20.12.2003)	
International Patent Classification (8th edition unless older edition indicated) Relevant information in Form PCT/ISA/237			
Applicant RFELD MIKROTECHNIK BTS GMBH			

This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).

This REPORT consists of a total of 9 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.

3. This report contains indications relating to the following items:

- |                                     |              |   |
|-------------------------------------|--------------|---|
| <input checked="" type="checkbox"/> | Box No. I    | Basis of the report   |
| <input type="checkbox"/>            | Box No. II   | Priority  |
| <input checked="" type="checkbox"/> | Box No. III  | Non-establishment of opinion with regard to novelty, inventive step and industrial applicability  |
| <input type="checkbox"/>            | Box No. IV   | Lack of unity of invention  |
| <input checked="" type="checkbox"/> | Box No. V    | Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement |
| <input type="checkbox"/>            | Box No. VI   | Certain documents cited   |
| <input type="checkbox"/>            | Box No. VII  | Certain defects in the international application  |
| <input type="checkbox"/>            | Box No. VIII | Certain observations on the international application   |

4. The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis .2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Date of issuance of this report 29 August 2006 (29.08.2006)
	Authorized officer  Yolaine Cussac  e-mail: pt11@wipo.int

# PATENT COOPERATION TREATY

TRANSLATION

PCT

From the  
INTERNATIONAL SEARCHING AUTHORITY

To:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis.1)

To:		Date of mailing (day/month/year)	See form PCT/ISA/210
Applicant's or agent's file reference <b>EMB 04 1018-WO</b>		FOR FURTHER ACTION See paragraph 2 below	
International application No. <b>PCT/EP2004/012172</b>	International filing date (day/month/year) <b>28.10.2004</b>	Priority date (day/month/year) <b>20.12.2003</b>	
International Patent Classification (IPC) or both national classification and IPC <b>G01N33/533, B01J19/00, B01F13/00</b>			
Applicant <b>EHRFELD MIKROTECHNIK BTS GMBH</b>			

1. This opinion contains indications relating to the following items:

- ☒ Box No. I      Basis of the opinion
- ☐ Box No. II      Priority
- ☒ Box No. III      Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV      Lack of unity of invention
- ☒ Box No. V      Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI      Certain documents cited
- ☐ Box No. VII      Certain defects in the international application
- ☐ Box No. VIII      Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/EP	Authorized officer
Facsimile No.	Telephone No.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/012172

Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.  
☐ This opinion has been established on the basis of a translation from the original language into the following language \_\_\_\_\_, which is the language of a translation furnished for the purposes of international search (under Rule 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
  - a. type of material  
☐ a sequence listing  
☐ table(s) related to the sequence listing
  - b. format of material  
☐ in written format  
☐ in computer readable form
  - c. time of filing/furnishing  
☐ contained in the international application as filed.  
☐ filed together with the international application in computer readable form.  
☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/012172

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application

☒ claims Nos. 8

because:

☐ the said international application, or the said claims Nos. \_\_\_\_\_  
relate to the following subject matter which does not require an international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. \_\_\_\_\_  
are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. \_\_\_\_\_ are so inadequately supported  
by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 8

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form

☐ has not been furnished

☐ does not comply with the standard

the computer readable form

☐ has not been furnished

☐ does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.

☐ See Supplemental Box for further details.



WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

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Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability:  
citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	—	YES
	Claims	1-7	NO
Inventive step (IS)	Claims	—	YES
	Claims	1-7	NO
Industrial applicability (IA)	Claims	1-7	YES
	Claims	—	NO

2. Citations and explanations:

Reference is made to the following documents:

D1: SPIKMANS VALERIE ET AL: "On-line on-chip post-column derivatisation reactions for pre-ionisation of analytes and cluster analysis in gradient microliquid chromatography/electrospray mass spectrometry." RAPID COMMUNICATIONS IN MASS SPECTROMETRY: RCM. 2002, vol. 16, no. 14, 2002, pages 1377-1388, XP009049801 ISSN: 0951-4198

D2: WO 96/40398 A (BIOSEPPRA INC) 19 December 1996 (1996-12-19)

D3: KLING KERSTIN ET AL: "Visualization of micro- and macromixing in liquid mixtures of reacting components" PROC. ASME/JSME JOINT FLUIDS ENG. CONF.; PROCEEDINGS OF THE ASME/JSME JOINT FLUIDS ENGINEERING CONFERENCE 2003, vol. 2 C, 2003, pages 2329-2335, XP009049802

D4: BRINKLEY M: "A BRIEF SURVEY OF METHODS FOR PREPARING PROTEIN CONJUGATES WITH DYES, HAPTENS, AND CROSS-LINKING REAGENTS"

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

PCT/EP2004/012172

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

BIOCONJUGATE CHEMISTRY, AMERICAN CHEMICAL  
SOCIETY, WASHINGTON, US, vol. 3, no. 1,  
January 1992 (1992-01), pages 2-13,  
XP000261480 ISSN: 1043-1802

D5: HAUGLAND R P: "COUPLING OF MONOCLONAL  
ANTIBODIES WITH FLUOROPHORES" METHODS IN  
MOLECULAR BIOLOGY, HUMANA PRESS INC.,  
CLIFTON, NJ, US, vol. 45, 1995, pages 205-  
221, XP009020645

1. Clarity (PCT Article 6)

The phrases "biomolecules" and "marker compound"  
in claim 1 are vague and unclear and leave the  
reader uncertain as to the meaning of the  
technical features in question. As a result, the  
subject matter of said claim is not clearly  
defined (PCT Article 6).

2. Novelty (PCT Article 33(1) and 33(2))

The present application does also not meet the  
requirements of PCT Article 33(1) because the  
subject matter of claims 1-7 is not novel under  
PCT Article 33(2).

2.1 Document D1 discloses (the references between  
parentheses relate to this document) a method for  
labeling biomolecules carrying free reactive  
groups (aldehydes and amines may be regarded as  
such, see also figure 1) by a marker compound



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Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

reacting therewith with formation of a covalent bond (see figures 4 and 5, TMPP+ is regarded here to be the "marker compound"), characterized in that solutions of both compounds are delivered in defined mass flows to a micromixer, preferably a static micromixer, the reaction mixture, where appropriate, is subsequently fed into a dwell structure and remains there for a time predetermined by the volume of said dwell structure and the flow rate of the reaction mixture, and the reaction is stopped after a time preset by the reaction conditions (see page 1378, left column, last paragraph - page 1378, right column, second paragraph, page 1379, and page 1381, right column - 1382, left column, second paragraph). With regard to D2, dependent claims 2, 4-7 do not appear to contain any additional features which, in combination with the features of any claim to which claims 2, 4-7 refer back, meet the EPC requirements for novelty and inventive step. Claim 3 is novel with regard to D1.

- 2.2 Document D2 likewise discloses a method according to claim 1. D2 discloses on-line detection of a biomolecule (protein, nucleic acid, etc., see claim 9, for example) by reaction with a fluorescent dye (page 14, line 29 - page 14, line 7), with use of a micromixer (see figure 1: systems 13, 33 and 31, and pages 13 and 14) and formation of a covalent bond (page 15, lines 20-25). With regard to D2, dependent claims 2-7 do

WRITTEN OPINION OF THE  
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International application No.

PCT/EP2004/012172

Box No. V

Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability;  
citations and explanations supporting such statement

not appear to contain any additional features which, in combination with the features of any claim to which claims 2-7 refer back, meet the EPC requirements for novelty and inventive step.

3. Document D3 discloses visualization of reactions in liquid mixtures which are mixed by a micromixer. Here, 2 markers are added, one of which undergoes a chemical reaction, while the second one is inert. The reacting marker is a starch iodine complex which is decolorized by sodium thiosulfate in the course of reaction visualization. Thus, the reacting marker does not form a covalent bond with the biomolecule, starch. D3 is therefore not prejudicial to the novelty of claim 1.

Documents D4 and D5 disclose the reactions carried out in the examples. Said reactions are not carried out using a micromixer, however. They are therefore not prejudicial to the novelty of present claims 1-7. The examples demonstrated the advantages of the claimed method (degree of labeling) over the "traditional" labeling methods in D4 and D5.

WRITTEN OPINION OF THE  
INTERNATIONAL SEARCHING AUTHORITY

International application No.

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Supplemental Box

In case the space in any of the preceding boxes is not sufficient.

Continuation of:

Box III

Claim 8 relates to an inordinately large number of possible devices. The subject matter of claim 8 does not contain any technical equipment features which would characterize the claimed device more precisely. The device according to claim 8 therefore appears unclear and too broadly worded (PCT Article 6) to the extent that it is impossible to conduct a meaningful search. Any micromixer essentially is within the scope of protection of claim 1.

Consequently, no expert opinion has been established for claim 8 in respect of novelty, inventive step and industrial applicability (PCT Rule 66.1(e)).

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